

What Is Claimed Is:

1. A method for preparing biodegradable, biocompatible microparticles comprising:

A) preparing a first phase comprising:

- (1) a biodegradable, biocompatible polymeric encapsulating binder, and
- (2) an active agent having limited water solubility, dissolved or dispersed in a first solvent;

B) preparing an aqueous second phase;

C) combining said first phase and said second phase under the influence of mixing means to form an emulsion in which said first phase is discontinuous and said second phase is continuous;

D) separating said discontinuous first phase from said continuous second phase; and

E) washing said discontinuous first phase with

- (1) water at a temperature in the range of from about 25°C to about 40°C, or
- (2) an aqueous solution comprising water and a second solvent for residual first solvent in said first phase, thereby reducing the level of residual first solvent to less than about 2% by weight of said microparticles.

2. The method of claim 1 further comprising a step of quenching between step C) and step D).

3. The method of claim 1 wherein said biodegradable, biocompatible polymeric encapsulating binder is selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.

0850679-050297

35

4. The method of claim 1, wherein said first solvent is a solvent blend of at least two mutually miscible organic solvents.

5. The method of claim 4 wherein one of said organic solvents is an ester.

6. The method of claim 5 wherein said ester is of the structure R^1COOR^2 wherein R^1 and R^2 are independently selected from the group consisting of alkyl moieties of from 1 to 4 carbon atoms.

7. The method of claim 6 wherein said ester is ethyl acetate.

8. The method of claim 4 wherein one of said organic solvents is benzyl alcohol.

9. The method of claim 4 wherein said solvent blend comprises ethyl acetate and benzyl alcohol.

10. The method of claim 1 wherein said second phase comprises a hydrophilic colloid.

11. The method of claim 10 wherein said hydrophilic colloid is poly(vinyl alcohol).

12. The method of claim 1 wherein said mixing means comprises a static mixer.

13. The method of claim 1 wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

08850679-050297

36

14. The method of claim 1 wherein said aqueous solution comprises water and a C₁-C₄ alcohol.

15. The method of claim 14 wherein said C₁-C₄ alcohol is ethanol.

16. A method for preparing biodegradable, biocompatible microparticles comprising:

- A) preparing a first phase comprising
 - 1) a biodegradable, biocompatible polymeric encapsulating binder selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing, and
 - 2) an active agent selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof dissolved or dispersed in a blend comprising ethyl acetate and benzyl alcohol, said blend being free from halogenated hydrocarbons;
- B) preparing a second phase comprising polyvinyl alcohol dissolved in water;
- C) combining said first phase and said second phase in a static mixer to form an emulsion in which said first phase is discontinuous and said second phase is continuous;
- D) immersing said first and said second phases in a quench liquid;
- E) isolating said discontinuous first phase in the form of microparticles; and
- F) washing said discontinuous first phase with an aqueous solution comprising water and ethanol, thereby reducing the level of benzyl alcohol to less than about 2% by weight of said microparticles.

08850679-050297

17. A microencapsulated drug prepared by a method for preparing biodegradable, biocompatible microparticles comprising:

- A) preparing a first phase comprising:
 - (1) a biodegradable, biocompatible polymeric encapsulating binder, and
 - (2) an active agent having limited water solubility, dissolved or dispersed in a first solvent;
- B) preparing an aqueous second phase;
- C) combining said first phase and said second phase under the influence of mixing means to form an emulsion in which said first phase is discontinuous and said second phase is continuous;
- D) separating said discontinuous first phase from said continuous second phase; and
- E) washing said discontinuous first phase with
 - (1) water at a temperature in the range of from about 25 °C to about 40 °C, or
 - (2) an aqueous solution comprising water and a second solvent for residual first solvent in said first phase, thereby reducing the level of residual first solvent to less than about 2% by weight of said microparticles.

18. The microencapsulated drug of claim 17 wherein the process further comprises a step of quenching between step C) and step D).

19. The microencapsulated drug of claim 17, wherein said first solvent is a solvent blend of at least two mutually miscible organic solvents.

20. Microencapsulated risperidone, 9-hydroxyrisperidone, or pharmaceutically acceptable salts thereof prepared by a process comprising:

A) preparing a first phase comprising:

- 1) a biodegradable, biocompatible polymeric encapsulating binder selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing, and
- 2) an active agent selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof, dissolved or dispersed in a blend comprising ethyl acetate and benzyl alcohol, said blend being free from halogenated hydrocarbons;

B) preparing a second phase comprising polyvinyl alcohol dissolved in water;

C) combining said first phase and said second phase in a static mixer to form an emulsion in which said first phase is discontinuous and said second phase is continuous;

D) immersing said first and second phases in a quench liquid;

E) isolating said discontinuous first phase in the form of microparticles; and

F) washing said discontinuous first phase with an aqueous solution comprising water and ethanol, thereby reducing the level of benzyl alcohol to less than about 2% by weight of said microparticles.

21. A pharmaceutical composition comprising biodegradable and biocompatible microparticles in a pharmaceutically acceptable carrier, said microparticles comprising:

a polymeric encapsulating binder having dispersed or dissolved therein an active agent, and

less than about 2% by weight residual solvent, wherein said residual solvent is residual derived from a solvent employed in the preparation of said microparticles.

5 22. The composition of claim 21 wherein said polymeric encapsulating binder comprises a polymeric matrix material selected from the group consisting of poly(glycolic acid), poly(d,l-lactic acid), poly(l-lactic acid), and copolymers of the foregoing.

10 23. The composition of claim 22 wherein said polymeric matrix material is a copolymer of poly(glycolic acid) and poly(d,l-lactic acid).

24. The composition of claim 23 wherein the content of said residual solvent is in the range of from about 0.5 to about 1.5% by weight.

15 25. The composition of claim 24 wherein said residual solvent is benzyl alcohol.

26. The composition of claim 25 wherein the molar ratio of lactide to glycolide is in the range of 85:15 to 50:50.

20 27. The composition of claim 25 wherein the microparticles comprise from about 1 to about 90 wt.% of said active agent.

28. The composition of claim 25 wherein the microparticles comprise from about 35 to about 40 wt.% of said active agent.

25 29. The composition of claim 25 wherein the microparticles range in size from about 1 to about 500 microns.

08860679-050297

40

30. The composition of claim 25 wherein the microparticles range in size from about 25 to about 180 microns.

31. The composition of claim 25 wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

32. A pharmaceutical composition comprising biodegradable and biocompatible microparticles, ranging in size from about 25 to about 180 microns, in a pharmaceutically acceptable carrier, said microparticles comprising:
a copolymer of poly(glycolic acid) and poly(d,l-lactic acid) wherein the molar ratio of lactide to glycolide is in the range of from about 85:15 to about 50:50 and having dispersed or dissolved therein from about 35 to about 40% of an active agent comprising risperidone, 9-hydroxy-risperidone, or pharmaceutically acceptable salts thereof, and

from about 0.5 to about 1.5% by weight of benzyl alcohol.

33. The method of claim 1, wherein said active agent comprises at least one basic moiety.

34. The microencapsulated drug of claim 17, wherein said active agent comprises at least one basic moiety.

35. The composition of claim 21, wherein said active agent comprises at least one basic moiety.

36. The composition of claim 25, wherein said active agent comprises at least one basic moiety.

08860679-050297

4/

37. A method of preparing biodegradable, biocompatible microparticles, comprising:

- A) preparing a first phase, said first phase comprising an active agent, a biodegradable, biocompatible polymer, and a first solvent;
- B) preparing a second phase, wherein said first phase is substantially immiscible in said second phase;
- C) flowing said first phase through a static mixer at a first flow rate;
- D) flowing said second phase through said static mixer at a second flow rate so that said first phase and said second phase flow simultaneously through said static mixer thereby forming microparticles containing said active agent;
- E) isolating said microparticles; and
- F) washing said microparticles with water at an elevated temperature or with an aqueous solution comprising water and a second solvent for residual first solvent in said microparticles, thereby reducing the level of residual first solvent to less than about 2% by weight of said microparticles.

38. The method of claim 37, wherein said first solvent comprises ethyl acetate and benzyl alcohol.

39. The method of claim 38, wherein said active agent comprises at least one basic moiety.

40. The method of claim 1, wherein said second phase comprises an aqueous solution of a hydrophilic colloid.

41. The method of claim 1, wherein said second phase comprises an aqueous solution of a surfactant.

42

42. The method of claim 1, wherein said second phase is water.

43. The microencapsulated drug of claim 17, wherein said second phase comprises an aqueous solution of a hydrophilic colloid.

44. The microencapsulated drug of claim 17, wherein said second phase comprises an aqueous solution of a surfactant.

45. The microencapsulated drug of claim 17, wherein said second phase is water.

46. The method of claim 1, wherein said first solvent is free from halogenated hydrocarbons.

47. The microencapsulated drug of claim 17, wherein said first solvent is free from halogenated hydrocarbons.

48. The method of claim 37, wherein said first solvent is free from halogenated hydrocarbons.

49. A method for preparing biodegradable, biocompatible microparticles, comprising:

- A) contacting microparticles comprising a biodegradable, biocompatible polymer matrix containing an active agent and an organic solvent with an aqueous washing system to thereby reduce the level of residual organic solvent to less than about 2% by weight of said microparticles, wherein said aqueous washing system is (1) at a temperature in the range of from about 25°C to about 40°C for at least part of step A, or (2) an aqueous solution

08850679-050297

43

comprising water and a water-miscible solvent for said organic solvent; and

B) recovering said microparticles from said aqueous washing system.

50. The method of claim 49, wherein said active agent is selected from the group consisting of risperidone, 9-hydroxyrisperidone, and pharmaceutically acceptable salts thereof.

51. The method of claim 49, wherein said organic solvent is a solvent blend of at least two mutually miscible organic solvents.

52. The method of claim 51, wherein said solvent blend comprises ethyl acetate and benzyl alcohol.

08850679-050297

10

44